PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ARUGA, Mitsuyuki
Kyodo Building
3-6, Nihonbashiningyocho 1-chome
Chuo-ku
Tokyo 103-0013
JAPON

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.05.2001
Applicant's or agent's file reference FP-MM-0025	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP00/00742	10/02/2000	10/02/1999

Applicant
MEIJI MILK PRODUCTS CO., LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Exner, K Tel.+49 89 2399-7826

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FP-MM-0025		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP00/00742	10/02/2000	10/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/122		
Applicant MEIJI MILK PRODUCTS CO., LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/08/2000	16.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Winger, R Telephone No. +49 89 2399 8129

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP00/00742

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-29 as originally filed

Claims, No.:

1-9 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☒ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 7-9 (industrial applicability).

because:

☒ the said international application, or the said claims Nos. 7-9 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-6
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Section III: Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 7-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V: Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Prior Art: Reference is made to the following documents cited in the International Search Report

D1: WO 99 08987: cited in the application
D2: TETRAHEDRON, vol. 54, 1998, pages 7735-7748
D3: METH. FIND. EXP. CLIN. PHARMACOLOGY, SUPPL. B, 1996, page 205
D4: WO 94 19493 A
D5: WO 96 21438 A
D6: EP-A-0 593 831
D7: WO 91 05754 A

2.1 Document D1, which was published after the claimed priority date, will be taken into account as long as no translated priority document is available.
Document D1 discloses the compounds of the current invention (e.g., examples) for the treatment of diseases caused by neural degeneration (e.g, Alzheimer). A neurite growth stimulating effect is shown.

2.2 Document D2 discloses the induction of neurite outgrowth by various cyclohexenoic alcohols (Table 1). On page 7742 it is stated that the presence of a methyl group in the cyclohexenoic ring plays an important role.

2.3 Document D3 discloses the use of SR 57746A, a substance mimicking or enhancing the effects of NGF on cell survival and neurite outgrowth, for the treatment of ALS.

2.4 Document D4 discloses neurodegenerative diseases like ALS and Alzheimer (claim 3), which are related to mutations in a SOD coding sequence (claim 1).

2.5 Document D5 discloses the medical use of compounds, differing from the current invention with respect to the length of the side chain.

2.6 Document D6 discloses derivatives of the compounds of the invention for the treatment of neurodegenerative diseases (claim 4).

2.7 Document D7 discloses compounds for the treatment of neurodegenerative diseases (claim 9), whereby on page 2 ALS is disclosed. The generic formula (claim 1) covers the compounds of the invention.

3. Novelty (Article 33(2) PCT):

3.1 Claim 1 relates to the medical use of a drug containing a cyclohexenone long chain alcohol. As the medical use of these compounds is anticipated by documents D1 and D2, the subject-matter of claims 1-3 does not seem to be novel.

3.2 Claim 2 relates to the use of the cyclohexenone long chain alcohol for the production of a preventive and therapeutic drug for a neurodegenerative disease, whereas claim 7 relates to the corresponding treatment. However, document D1 anticipates a corresponding use and thus the subject-matter of claims 4-9 does not seem to be novel (the selection of ALS seems to be arbitrary (non-purposive selection); Alzheimer is a disease related to mutations in SOD genes (document D4)).

In addition, the selection of certain compounds of document D7 for the treatment of certain neurodegenerative diseases does not seem to associated with any unknown effect, and thus this selection does not seem to be novel.

4. Inventive Step (Article 33(3) PCT):

The current invention relates to the use of cyclohexenone long chain alcohols for the treatment of neurodegenerative diseases, especially ALS and disorders caused by mutations in a SOD gene.

Document D2, which is considered to represent the closest prior art, discloses an neurite outgrowth enhancing effect, thus differing with respect to the selection of certain diseases.

However, taking into account that document D3 discloses the use of neurite outgrowth enhancers for the treatment of ALS, the use of said outgrowth enhancing substances for the treatment of ALS seems to be obvious, and thus, the subject-matter of claims 1-9 does not seem to be inventive.

In addition, the disclosure of document D2, which indicates that a methyl group in the ring plays an important role, seems to render it improbable that all compounds of the invention solve the problem.

5. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claims 1-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Section VII: Certain defects in the international application

6. The obtained compound on page 8, line 13, should not be (12).

7. The last phrase on page 27 (prolonged by 161 to 180 days) seems to be unclear.

Re Section VIII: Certain observations on the international application

8. The terms "neurodegenerative disease" (see page 1) and "disorders caused by mutation in a SOD gene" are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of claims 1, 3, 4, 6, 7, and 9 unclear (Article 6 PCT).